

REVIEW ARTICLE

Strategic Use of Intravenous Medications to Protect Target Organs in Hypertensive Emergencies

Mariana Costa Silva¹, Rubens Carmo Costa-Filho^{2,3}  Vanessa Estado^{1,2}

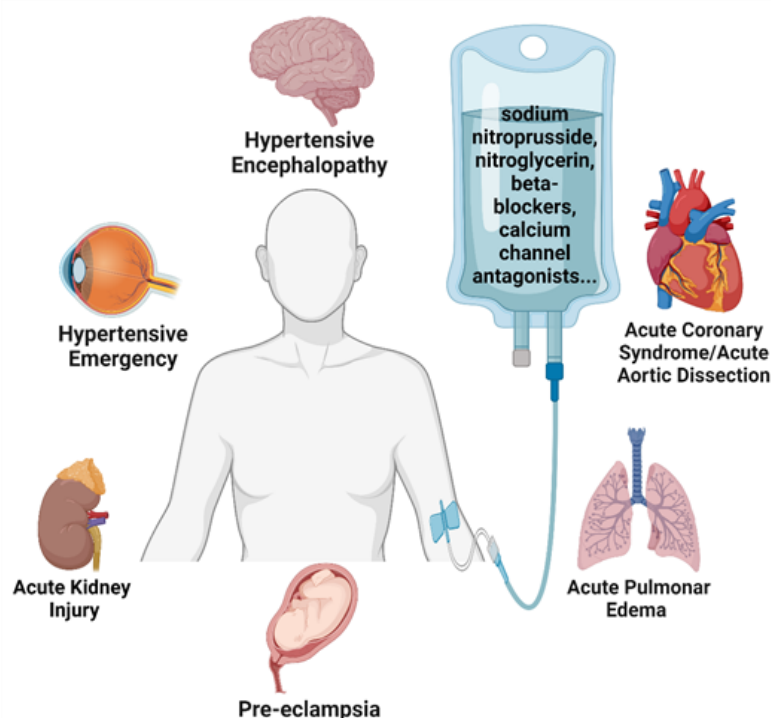
Estácio de Sá University, IDOMED,¹ Rio de Janeiro, RJ – Brazil

Laboratory of Immunopharmacology, FIOCRUZ,² Rio de Janeiro, RJ – Brazil

IMUNOFAR, Technological Platform for Coagulation Studies, Fiocruz, Rio de Janeiro,³ RJ – Brazil

Central Illustration: Strategic Use of Intravenous Medications to Protect Target Organs in Hypertensive Emergencies

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Intravenous treatment strategy for HE, focusing on the protection of vulnerable organs, including during pregnancy. The image highlights AOD in the brain, heart, kidneys, eyes, and lungs, corresponding to conditions such as hypertensive encephalopathy, acute coronary syndrome/aortic dissection, acute kidney injury, hypertensive retinopathy, acute pulmonary edema, and pregnancy-related complications like preeclampsia. The intravenous medication bag denotes drug classes such as sodium nitroprusside, NTG, beta-blockers, calcium channel antagonists (including dihydropyridines like clevidipine), and dopamine-1 receptor agonists like fenoldopam. All these drugs are designed to rapidly and effectively reduce BP, thereby preventing further organ damage.

Keywords

antihypertensive agents; adrenergic beta-antagonists;
calcium channel blockers; cardiovascular diseases;
hypertensive crisis.

Mailing Address: Rubens Carmo Costa-Filho

FIOCRUZ, Praça Atahualpa, 60, 310. Postal code: 22441-130. Rio de Janeiro, RJ – Brazil

E-mail: rubens1956@gmail.com

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Abstract

Hypertensive emergencies (HE) are life-threatening conditions triggered by sudden increases in blood pressure (BP) exceeding 180 mmHg systolic and/or 110 mmHg diastolic levels, often resulting in acute organ damage (AOD) and the risk of death. This article discusses contemporary practices in diagnosing and managing these episodes, emphasizing early recognition and immediate therapeutic intervention. It highlights the significance of a meticulous diagnostic assessment for appropriate clinical and therapeutic approaches, including detailed medical history, physical examination, and complementary investigations. Treatment focuses on the judicious use of intravenous antihypertensive agents such as sodium nitroprusside, nitroglycerin (NTG), beta-blockers, and calcium channel antagonists, stressing careful administration to prevent further harm. Individualization of treatment in HE is imperative and should be meticulously tailored to the patient's clinical profile and main complications, notably hypertensive encephalopathy, acute pulmonary edema, acute coronary syndromes, acute aortic dissection, and preeclampsia. These conditions require differentiated approaches due to their severity. The article underscores the scarcity of randomized controlled clinical trials addressing all daily practice questions regarding managing HE. This is due to the complexity of available drugs, clinical conditions, adverse effects, and drug interactions in various scenarios.

Consequently, clinical wisdom and careful observation remain pivotal in decision-making. It also addresses the complexity of accurately measuring BP in emergency settings, which can pose an additional diagnostic challenge. Finally, it emphasizes the need for new evidence to guide therapeutic practices in HE, aiming to improve patient care and clinical outcomes continuously.

Definition and Diagnostic Criteria

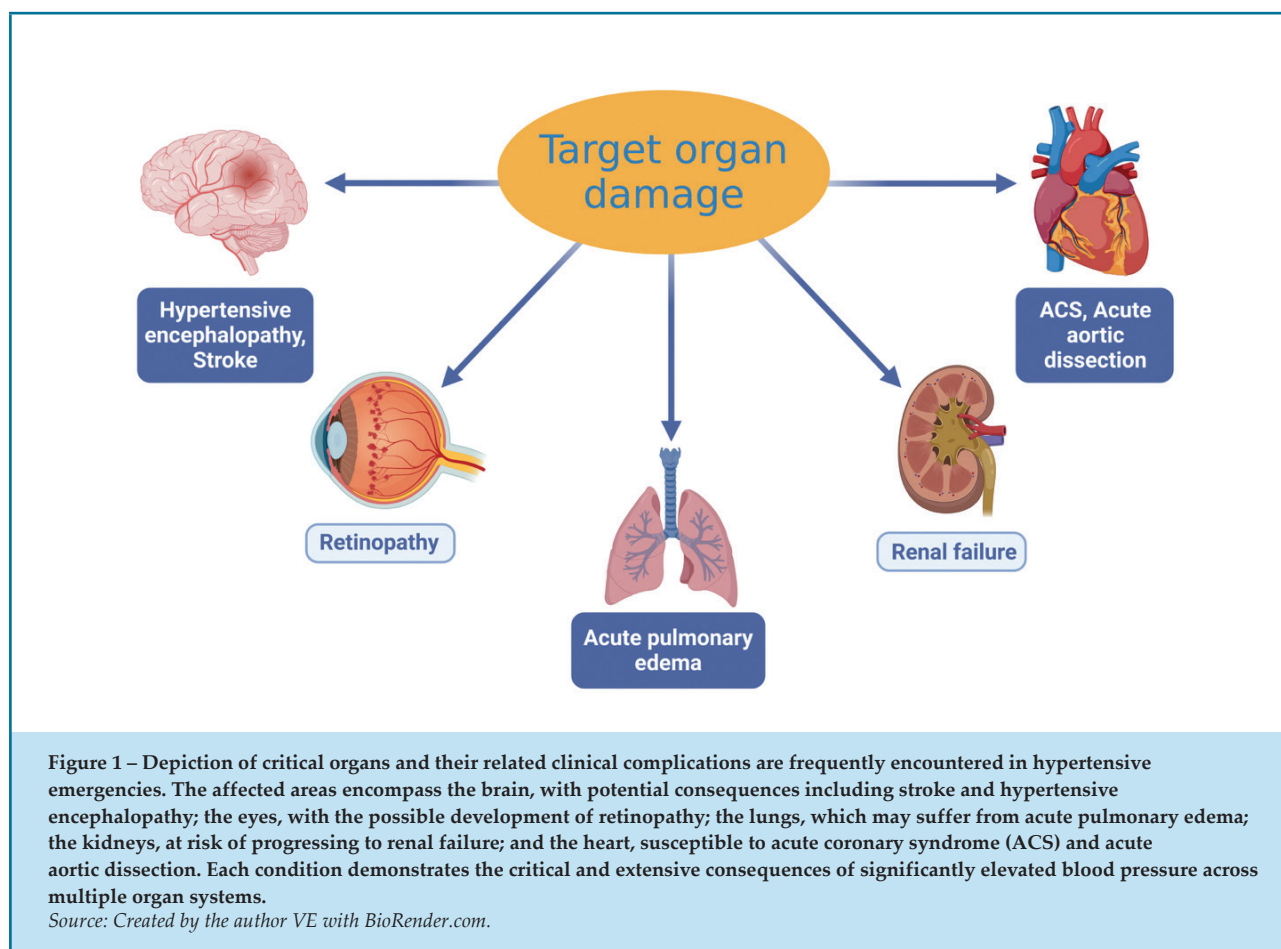
Hypertensive emergencies (HE) are characterized by acute elevations in systolic blood pressure (SBP) to values equal to or greater than 180 mmHg and/or diastolic blood pressure (DBP) to 110 mmHg or higher (category 3), which are associated with acute organ damage (AOD) and immediate potential risk of death.¹⁻³ The most affected organ systems are neurological, cardiovascular, and renal (Figure 1). It is essential to emphasize that a mere increase in blood pressure (BP) does not constitute

an emergency unless there is associated AOD. Acute cerebral, cardiovascular, hematological, renovascular, or ophthalmological injuries require prompt intervention to reduce BP and prevent further harm.⁴ The most common manifestations of HE include stroke and acute pulmonary edema.⁵ Recognizing the severity and absolute values of BP elevation is vital for early diagnosis and effective intervention, aiming for a favorable prognosis for the patient.

In contrast to HE, hypertensive urgencies,³ a term traditionally used to describe symptomatic increases in BP without organ damage, are now recognized as “uncontrolled hypertension.” Patients in this category do not require hospitalization but rather a rigorous outpatient follow-up to achieve BP control.⁵ Hypertensive urgency and emergency must be distinguished from the pseudo-hypertensive crisis, which is characterized by a transient elevation of BP in response to painful or emotional events, such as headache, postural vertigo, anxiety, or panic syndrome.⁶

Recent evidence underscores the importance of lowering early and intensive BP to mitigate hematoma expansion and improve clinical outcomes in acute intracerebral hemorrhage. Studies like INTERACT-2⁷ (Intensive BP Reduction in Acute Cerebral Hemorrhage Trial 2) and ATTACH-2⁸ (Antihypertensive Treatment of Acute Cerebral Hemorrhage 2) highlight that achieving target SBP levels of around 130–140 mmHg, initiated as soon as possible using continuous intravenous infusion of nicardipine, significantly reduces the risks of death and major disability. Similarly, well-designed prospective studies have demonstrated the critical impact of BP management on patient outcomes, emphasizing the benefits of rapid and stable BP control in minimizing hematoma growth and reducing mortality and disability.

In summary, three rules of BP management (fast, intense, and stable)⁹ should be considered for patients with acute intracerebral hemorrhage to provide maximal protection against hematoma expansion and subsequent poor prognosis. Although Neurology has identified various issues through multiple studies, more research is needed to answer the broad and complex questions regarding organ damage caused by severe hypertension. Nonetheless, the triple rule that is composed of these factors—Fast: initiate BP lowering treatment using intravenous infusion as soon as possible; Intense: achieve target SBP < 140 mm Hg (130 mm Hg if possible) as soon as possible; Stable: maintain stable control of SBP to optimize patient prognosis—may serve as a valuable guideline to



help steer bedside management and optimize patient outcomes.

Definitions of Hypertensive Urgencies and Emergencies (2023 Guideline)

HE are characterized by a critical elevation of BP, categorized as grade 3, which concurrently presents with acute injuries to vital organs, establishing a framework of AOD.³ These are potentially life-threatening conditions demanding immediate intervention to reduce BP, typically through intravenous therapy (Table 1).³ The speed at which the BP elevation occurs can be as crucial as the maximum value attained in assessing clinical severity and the extent of damage to vital organs.³

Typical Clinical Presentations of HE

1. Severe hypertension is associated with conditions necessitating intensified BP management, such as acute stroke (hemorrhagic or ischemic/thromboembolic), aneurysm or aortic dissection, acute heart failure,

acute coronary syndrome, and acute renal failure. These emergent conditions can occur even with modest increases in BP, which is sufficient to precipitate organ failure.

2. Hypertension induced by pheochromocytoma or the use of exogenous sympathomimetic substances, such as the abuse of drugs like methamphetamine or cocaine, can lead to rapid and severe elevations in BP. This condition can progress to a hypertensive emergency when accompanied by evidence of acute target organ damage.

3. Severe forms of hypertensive disorders of pregnancy, including preeclampsia/eclampsia accompanied by HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet count), represent a hypertensive emergency. Malignant hypertension, with or without the presence of thrombotic microangiopathy or acute renal failure, is characterized by fibrinoid necrosis in small arteries, affecting organs such as the kidneys, retina, and brain. Emergency symptoms vary depending on the affected organ and may include headaches, visual disturbances,

Table 1 – Intravenous agents, onset and duration of action, dosage, and pharmacological considerations for the immediate treatment of HE.

Drug	Onset of action	Effect Duration	Dosage	Contraindications	Adverse effects	First-line treatment (*HE)
Esmolol	1 min	10–30 min	0.5–1 mg/kg i.v. bolus. 50–300 µg/kg/min i.v. infusion	Second or third-degree atrioventricular block, systolic heart failure, asthma, bradycardia	Bradycardia	Acute aortic dissection
Metoprolol	1–2 min	5–8 h	2.5–5 mg i.v. bolus over 2 min; may repeat every 5 min to a maximum dose of 15 mg	Second or third-degree atrioventricular block, systolic heart failure, asthma, bradycardia	Bradycardia	Acute aortic dissection
Labetalol	5–10 min	3–6h	10–20 mg i.v. bolus in 1 min; incremental doses of 20 mg may be administered i.v. at 10 min intervals (max 80 mg) or 1–3 mg/min i.v. infusion until goal BP is reached	Second or third-degree atrioventricular block, systolic heart failure, asthma, bradycardia	Bronchoconstriction, fetal bradycardia	Malignant hypertension with or without renal failure, hypertensive encephalopathy, acute aortic dissection, acute coronary event, severe eclampsia or preeclampsia/HELLP*
Nicardipine	5–15 min	4–6 h	5–15 mg/h i.v. infusion, starting dose 5 mg/h, increase every 15–30 min with 2.5 mg until goal BP (maximum 15 mg/h)	Liver failure	Headache, reflex tachycardia	Malignant hypertension with or without renal failure, hypertensive encephalopathy, severe eclampsia or preeclampsia/HELLP*
NTG	1–5 min	5–10 min	5–200 µg/min i.v. infusion, 5 µg/min, increase every 5 min		Headache, reflex tachycardia	Acute coronary event, acute cardiogenic edema, acute aortic dissection
Nitroprusside	Immediate	1–3 min	0.3–0.5 µg/kg/min i.v. infusion, increase by 0.5 µg/kg/min every 5 min until goal BP (maximum dose 10 µg/kg/min)	Liver/kidney failure (relative)	Cyanide intoxication	Cardiogenic acute edema, acute aortic dissection
Clevidipine	2–4 min	5–15 min	1–2 mg/h i.v. infusion, double the dose at 90-second intervals initially (maximum dose 32 mg/h)	Severe aortic stenosis	Reflex tachycardia, headache	Acute perioperative hypertension, HE

			0.1–0.3 µg/kg/min i.v. infusion, increase by 0.05–0.1 µg/kg/min every 15 min (maximum dose 1.6 µg/kg/min)	Glaucoma, sulfite allergy	Headache, flushing, tachycardia	HE, acute renal failure
Fenoldopam	< 5 min	30–60 min				

This table provides detailed information on the primary intravenous medications used in HE, including their onset of action, duration of effect, recommended dosages, contraindications, and adverse effects. It also highlights the specific clinical scenarios where each medication is indicated as first-line treatment. *HE: Hypertension Emergencies; Photosensitive Drug; +HELLP: HELLP syndrome is a severe pregnancy complication characterized by hemolysis, elevated liver enzymes, and a low platelet count. The pathophysiology of HELLP syndrome is not fully understood, but it involves vascular endothelial damage and activation of the coagulation cascade, leading to microangiopathic hemolytic anemia, hepatic dysfunction, and thrombocytopenia. Symptoms may include malaise, upper abdominal pain, nausea, vomiting, headache, and visual disturbance. Management often necessitates the delivery of the fetus, regardless of gestational age, especially in severe cases or when there is evidence of end-organ damage or a threat to the life of the mother or fetus. Postpartum recovery requires close monitoring and supportive care. Source: Adapted from Mancia et al.³
I.V.: intravenous; HE: hypertensive emergencies; BP: blood pressure; HELLP: hemolysis, elevated liver enzymes, low platelet; NTG: nitroglycerin.

photopsia, dizziness, neurological deficits, chest pain, and dyspnea. Manifestations such as hypertensive encephalopathy, drowsiness, lethargy, tonic-clonic seizures, and cortical blindness may precede loss of consciousness. Focal neurological lesions are rare but can be indicative of acute stroke.

"Hypertensive urgency" describes severe hypertension without evidence of AOD. The extent of hypertensive urgencies is not well-defined, primarily due to the different criteria used for its definition. The ambiguity between "hypertensive urgency" and "hypertensive crisis" has influenced epidemiological data.³

Objective

The main objective of this article was to provide a detailed review of the strategic use of intravenous medications in HE, focusing on protecting target organs and reducing mortality and morbidity.

Methodology

To conduct this review, we adopted a systematic bibliographic search approach. Searches were conducted in the PubMed, Scopus, and Web of Science databases using specific descriptors such as "HE," "intravenous antihypertensives," and "AOD." Article selection included studies published between 2000 and 2023, emphasizing systematic reviews, meta-analyses, and randomized clinical trials. Articles not available in English or Portuguese were excluded.

The appropriate approach to HE is crucial for protecting target organs and minimizing long-term damage. The strategic use of intravenous medications plays a vital role in this context, allowing for rapid

titration of BP and targeted action on the most vulnerable organs, such as the brain, heart, and kidneys. The central goal of this management is to stabilize the patient as quickly as possible in a hospital setting (intensive care unit, ICU) to preserve organ function and prevent fatal complications.^{3,10} To ensure an effective and safe therapeutic approach, the selection of pharmacotherapy in managing HE should be based on well-established scientific evidence,¹¹ a thorough analysis of the clinical presentation, and a deep understanding of the pharmacodynamics and pharmacokinetics of therapeutic options (Table 1). Furthermore, adopting rigorously established clinical protocols reflecting contemporary guidelines helps minimize medical practice variability and reinforces patient management uniformity. Continuous monitoring of vital parameters is imperative, not only for optimizing clinical outcomes but also for promoting maximum safety during patient treatment.

Initial Diagnostic Approach in HE

The initial clinical evaluation in cases of HE is paramount. It should be comprehensive and rapid, encompassing the patient's medical history, a thorough physical examination, and, when indicated, imaging studies aiming to reduce associated morbidity and mortality (Table 2). The detailed collection of the medical history should focus on the duration and severity of pre-existing hypertension and the identification of prior target organ injuries. It is crucial to conduct a meticulous investigation into the previous use of antihypertensive medications¹ and their effectiveness in historical BP control, as well as identifying the use of other substances that may affect BP levels. BP measurement in the supine and orthostatic positions in both arms is recommended to rule out pathological

Table 2 – Specific exams for each type of hypertensive emergency.

HE	Diagnostic Work-Up Of Hypertension Emergencies
Acute Pulmonary Edema	Serum brain natriuretic peptide (BNP) if available, echocardiogram
Acute Coronary Syndrome	Markers of myocardial necrosis (always), coronary angiography (almost always)
Acute Aortic Dissection	Computed tomography, transesophageal echocardiogram, magnetic resonance angiography, angiography
Hypertensive Encephalopathy	Head computed tomography (to rule out stroke)
Stroke	Head computed tomography
Pre-Eclampsia	Elevated lactate dehydrogenase, presence of microangiopathic hemolytic anemia, elevated liver transaminases, proteinuria ≥ 2 g in 24 h, creatinine > 1.2 mg/dL, SBP ≥ 160 mmHg, or DBP ≥ 110 mmHg
Drug-Induced Hypertensive Crisis	Toxicology screen (urine or blood), electrocardiogram, serum electrolytes, renal function tests, liver function tests, head computed tomography (if neurological symptoms are present)

This table outlines the specific diagnostic work-up required for different HE. It includes recommended exams and tests to accurately diagnose and manage each condition. Source: Created by the authors. HE: Hypertensive emergencies

conditions such as aortic dissection, which can manifest significant discrepancies in BP between limbs.¹² This practice should be complemented by careful palpation of arterial pulses in all extremities, thus ensuring a comprehensive vascular assessment.

Complementary Tests

A series of ancillary examinations are indispensable in managing HE and urgencies. Standard tests, forming the cornerstone of diagnostic evaluation, include:

- Fundoscopy to assess vascular changes in the fundus of the eye.
- 12-lead electrocardiogram—crucial for detecting cardiac abnormalities.
- Complete blood count, encompassing hemoglobin and platelet counts, fibrinogen evaluation, and peripheral smear examination to detect hematological alterations.
- Assessment of renal function through creatinine, estimated glomerular filtration rate, electrolytes, lactate dehydrogenase, and haptoglobin to assess tissue damage.
- Urinary albumin-creatinine ratio and urinary microscopy, searching for erythrocytes, leukocytes, and/or cylinders that may indicate nephropathy.
- Pregnancy testing in women of childbearing age to exclude obstetric complications.

Additionally, specific tests are performed based on the patient's clinical presentation and diagnostic suspicion:

- Troponin and prohormone N-terminal pro-brain natriuretic peptide (NT-ProBNP) in cases of suspected heart failure and/or acute coronary syndrome.
- Chest radiography or ultrasound to identify pulmonary congestion and fluid overload.
- Echocardiography to assess heart failure, acute ischemia, or aortic dissection.
- Chest and/or abdominal computed tomography angiography is used to diagnose aortic disease, such as dissection.
- Brain computed tomography or magnetic resonance imaging to investigate nervous system involvement.^{13,14}
- Renal ultrasound in cases of renal impairment or suspected renal artery stenosis.
- Urine collection for detection of substances, such as cocaine or methamphetamine.

Comparisons with previous tests are valuable to identify the progression of target organ damage.¹³ In situations of altered mental status or markedly elevated BP, performing brain computed tomography or magnetic resonance imaging is imperative to exclude hemorrhage or hypertensive encephalopathy. This comprehensive and stratified approach ensures

precise assessment and effective treatment of acute hypertensive conditions.

Individualized Pharmacological Strategies

The treatment of HE based on the patient's clinical condition is illustrated in Figure 2. The ideal medication for the management of HE should be fast-acting, reversible, and have minimal side effects. However, defining a pharmacological agent that meets all these criteria is challenging, and choosing the most suitable medication for these situations remains uncertain. The lack of robust studies and evidence from randomized, double-blind clinical trials confirming the efficacy of antihypertensive drugs in reducing morbidity and mortality complicates the decision-making process.⁴ Nonetheless, based on clinical experience and observed outcomes, antihypertensive treatment is believed to be beneficial and can reduce mortality. Several critical studies have supported the use of intravenous antihypertensives. The Efficacy Study of Clevidipine Assessing its Preoperative Antihypertensive Effect in Cardiac Surgery (ESCAPE 1) trial,¹⁵ a randomized, double-blind, placebo-controlled study involving 105 heart surgery patients, demonstrated a >15% reduction in BP with clevidipine compared to placebo (82.7 vs. 7.5%, $p < 0.0001$). The Efficacy Study of Clevidipine Assessing its Postoperative Antihypertensive Effect Surgery-2 (ESCAPE 2) trial,¹⁶ double-blind and placebo-controlled, assessed clevidipine's efficacy and safety in hypertensive patient's post-heart surgery. Clevidipine significantly outperformed placebo, reducing BP by 5.7 vs. 0.1 mm Hg ($p < 0.0001$), with an onset of action within 2 minutes.

The Evaluation of the Ultra-Short-Acting Clevidipine in the Treatment of Patients with Severe Hypertension (VELOCITY) trial,^{17,18} a multicenter, open-label, quasi-trial, evaluated clevidipine's safety and BP control in 126 hypertensive patients in emergency and intensive care settings. The study showed a 6% BP reduction within the first 3 minutes and a total 15% reduction after 9.5 minutes, with a 27% reduction after 18 hours of infusion. It also demonstrated safety for patients with renal and heart failure.

The Efficacy Study of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events (ECLIPSE) trial,¹⁹ a multicenter, randomized, non-blinded study, evaluated 1,512 patients with

perioperative hypertension. Clevidipine was compared to nifedipine, nitroglycerin (NTG), and sodium nitroprusside (SNP). Clevidipine showed superior BP control with fewer fluctuations compared to NTG and SNP, and it reduced 30-day mortality rates compared to SNP (4.7 vs. 1.7%)¹⁹ However, this difference was not statistically significant after adjusting for confounding factors. The ECLIPSE trial, corroborating the results in other trials (ESCAPE 1 and 2 and VELOCITY), demonstrated clevidipine's safety and effectiveness for acute hypertension therapy, with reduced pressure fluctuations compared to NTG and SNP, the drugs most used in Brazil for rapid pressure control.²⁰

Patients with HE are typically admitted to ICUs, treated with intravenous and antihypertensives, and closely monitored (Table 3). General guidelines include reducing mean BP by up to 25% in the first hour and achieving a BP between 160/100–110 mmHg in the next 2–6 hours to reach a BP of 135/85 mmHg in the subsequent 24–48 hours^{1,3} (Figure 2).

Uncertainties and Challenges in BP Measurement in Emergency Settings

In the emergency room, BP measurements often do not adhere to guidelines and can be inaccurate. Elevations in BP are expected, with hypertensive values observed in 48% of patients referred to the emergency department within one year.²¹ The clinical relevance of these elevations is not entirely clear, as in many patients, high BP normalizes after the relief of pain, stress, and anxiety associated with an alert reaction. However, some studies have not found a close relationship between BP and pain, stress, or anxiety in the emergency setting. Furthermore, although BP measurements in the emergency room are generally not recommended for cardiovascular risk stratification, an association has been reported between BP measured in the emergency room and cardiovascular outcomes. It is essential to investigate whether there has been prior use of medications or substances that may cause an increase in BP or counteract the reduction in BP due to treatment. If BP is not severely elevated and the clinical picture does not suggest a hypertensive emergency, unassisted BP measurements should be taken with the patient alone in a calm environment, as such measurements typically do not trigger an alert reaction. BP measurements should be repeated at least at 1-hour intervals, and evidence suggests that in 30% of

Table 3 – Evidence-Based Intravenous Antihypertensive Treatments for Critical Hypertensive Conditions.

Drug of Choice	Condition	Dosage	Author
Esmolol, Labetalol	Acute aortic dissection	Esmolol: 500–1000 mcg/kg/min loading dose, 50 µg/kg/min infusion, maximum 200 µg Labetalol: 20 mg intravenous over 2 min, repeat or double every 10 min, up to 300 mg	29,45,8
NTG, Clevidipine, Nitroprusside	Acute pulmonary edema	NTG: 5–20 µg/min Nitroprusside: 0.3–0.5 µg/kg/min, maximum 10 mcg/kg/min Clevidipine: 1–2 mg/h, maximum 32 mg/h	29,45,51
Esmolol, NTG	Acute myocardial infarction, Unstable angina pectoris	Esmolol: same as above NTG: same as above	43,51
Clevidipine, Fenoldopam, Nicardipine	Acute renal failure intracerebral hemorrhage	Fenoldopam: 0.1–0.3 µg/kg/min, maximum 1.6 µg/kg/min Nicardipine: 5–30 mg/h, increments of 2.5 mg/h every 15 minutes as needed, with a maximum dose of 15 mg/h	29
Hydralazine, Labetalol	Eclampsia, Pre-eclampsia	Hydralazine: 20 mg intravenous, repeat every 4–6 h if needed Labetalol: 0.3–1.0 mg/kg, maximum 20 mg, followed by 0.4–1.0 mg/kg/h, maximum cumulative dose 300 mg	19,29
Clevidipine, Esmolol, NTG, Nicardipine	Postoperative surgical hypertension	Dosages as above for each drug	52
Clevidipine, Nicardipine, Phentolamine	Pheochromocytoma crisis, Hyperadrenergic state	Phentolamine: 5 mg intravenous bolus, repeat every 10 min as needed	45
Enalaprilat	High plasma renin state	1.25 mg intravenous over 5 min Repeat up to 5 mg every 6 h as needed	53
Clevidipine	Acute heart failure with hypertension	As above for clevidipine	51
Nicardipine, Labetalol	Hypertensive emergency in Emergency Department	Nicardipine: 5–30 mg/h Labetalol: 0.3–1.0 mg/kg	52,54

This table provides a detailed guide on the use of intravenous antihypertensive drugs for various HE. It lists the drugs of choice, the specific conditions they are used for, the recommended dosages, and the respective authors who recommend these treatments. This format helps practitioners make informed decisions on appropriate antihypertensive therapy in critical settings. Source: Created by the authors.

NTG: nitroglycerin

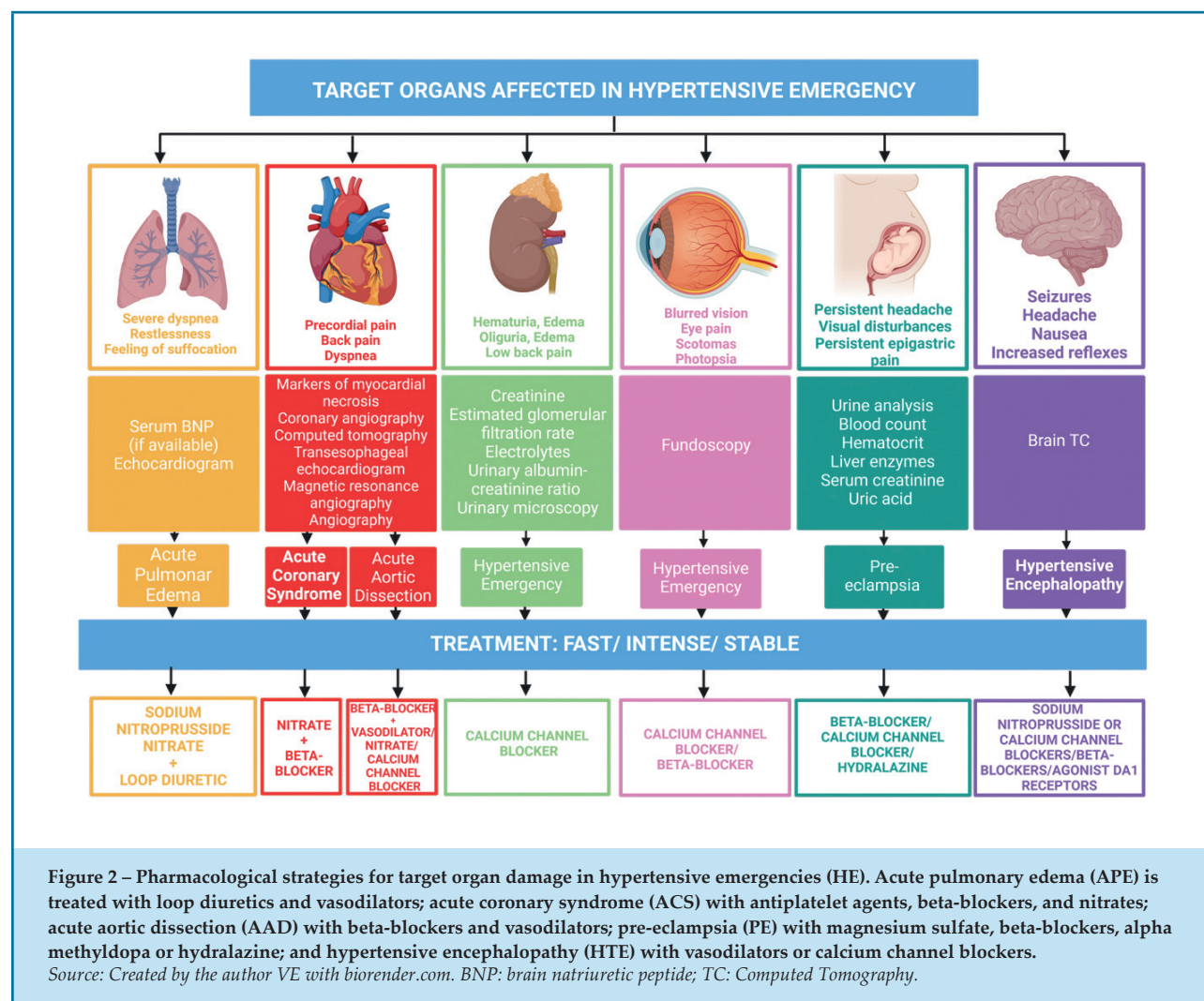
patients, BP decreases to grade 2 or lower values within 30 minutes.²²

Another category of hypertensive crisis, though rarely addressed in the literature and clinical practice, is the pseudo-hypertensive crisis. Its definition was established in Brazilian literature during the Multicenter Meeting on Hypertensive Crises²³ and in the 7th Brazilian Guideline of Arterial Hypertension,²⁴ describing it as a transient elevation of BP.

A notable retrospective study by Pierin et al.⁶ involving over 500 patients treated for hypertensive crises in the emergency room identified that the majority of patients were female, with an average

age in the fifth decade of life. Patients with HE were significantly older than those with hypertensive urgencies and pseudo-hypertensive crises, though there was no significant difference in sex among these categories. Epidemiological data provided by the authors were as follows:

- Hypertensive Emergency: Mean age 62.7, standard deviation $\pm$ 12.9 years (Initial BP measurement: elevated, with mean SBP of 214.8 $\pm$ 29.2 mmHg and DBP of 130.8 $\pm$ 14.9 mmHg).
- Hypertensive Urgency: Mean age 54.6 $\pm$ 14.0 years (Initial BP measurement: moderate, with mean SBP of 197.2 $\pm$ 23.6 mmHg and DBP of 124.9 $\pm$ 9.2 mmHg).



- Pseudo-hypertensive Crisis: Mean age 52.0±13.4 years (Initial BP measurement: transient, with mean SBP of 197.7±22.9 mmHg and DBP of 124.5±8.1 mmHg).

The p-value for age comparison was <0.001, highlighting the significant age differences among these groups. Also, the p-value for SBP and DBP comparisons between the groups was <0.001, further underscoring the substantial differences in BP readings among the hypertensive emergency, urgency, and pseudo-hypertensive crisis groups. This detailed stratification enriches the epidemiological analysis of hypertensive crises in the Brazilian context.

Definition and Epidemiology of HE

The therapeutic approach to HE, condition that trigger AOD and potential lethality, was simplified by introducing the acronym BARKH, which identifies

the most frequently affected organs: Brain, Arteries, Retina, Kidneys, and Heart (Figure 1). Although BARKH²⁵ contributes to the immediate identification and management of HE, it has limitations as it does not encompass all clinical possibilities of organ damage and is not described in the latest guidelines.³ When defined by acute organ injury, HE is low, occurring in approximately 0.5% of patients.²⁶ The stability of this rate over the past two decades contrasts with higher prevalence in developing nations, where hypertension affects a population exceeding one billion individuals. HE is associated with significant mortality, approaching 4%, with elevated BP levels being determinants in the progression of organ damage and patient prognosis. Incidence data from emergency services indicate that HE are more prevalent in older adults, with a higher incidence in males and individuals of lower socioeconomic status.²⁷ Therefore, the emphasis is placed on prompt clinical

recognition with swift intervention, establishing targeted therapeutic strategies to minimize organ damage and optimize patient clinical outcomes (Table 3).

Strategy for the Use of Intravenous Antihypertensives in HE

Sodium Nitroprusside

SNP is a vasodilator that acts on arterial and venous vessels, reducing pre- and afterload. It releases nitric oxide, increasing the formation of cyclic guanosine monophosphate in vascular smooth muscle cells, promoting relaxation and vasodilation. Administered by continuous infusion at a dosage of 0.25 to 10 µg/kg/min intravenously, it has an immediate onset of action and a duration of 1–2 minutes. SNP is indicated for various HE, including malignant hypertension, hypertensive encephalopathy, and stroke. However, its side effects and precautions include the risk of cyanide poisoning, the development of severe hypotension, and the occurrence of nausea and vomiting. It should be used cautiously in patients with renal or hepatic insufficiency and those with elevated intracranial pressure. Protecting the drug from light is essential during administration due to its photosensitivity.²⁸ Cyanide poisoning can be treated with hydroxocobalamin, which binds to cyanide to form cyanocobalamin. The typical dose for adults is 70 mg/kg intravenously, equivalent to 5 grams. Adverse effects may include skin reactions and nausea. Sodium thiosulfate is an alternative that aids in the elimination of cyanide from the body. The standard adult approach involves administering 300 mg of sodium nitrite and 12.5 grams of sodium thiosulfate intravenously. Combined use with hydroxocobalamin is not recommended (Table 3).

Calcium Channel Blockers and Fenoldopam in HE

Calcium channel blockers, including clevidipine and nicardipine, are fundamental in managing HE. These drugs act specifically by inducing arterial vasodilation, contributing to the rapid reduction of BP, a critical aspect in emergencies. **Fenoldopam**, a selective dopamine type-1 receptor agonist, promotes vasodilation in the renal and cerebral areas, rapidly lowering BP. However, its use requires caution in patients with glaucoma due to the risk of increased intraocular pressure.

In Brazil, the preference for SNP is often due to healthcare professionals' familiarity with this medication and its availability in the market. However, clevidipine

and nicardipine have comparable efficacy and ease of dosage adjustment⁴. It is essential to emphasize that the use of diuretics in hypertensive crises should be avoided due to their variable effect on volume status.¹

Nicardipine and clevidipine are established agents in the management of HE, such as preeclampsia, where rapid stabilization of BP is crucial. These drugs are effective at controlling BP and safe for both the mother and the fetus. Calcium channel blockers like nicardipine offer the benefit of BP control without significantly reducing uteroplacental blood flow, a vital aspect in this clinical context.³ The choice of a calcium channel blocker in HE should be individualized, considering the drug's efficacy, the patient's clinical characteristics, and available resources. This decision should be based not only on the clinical effectiveness of the agents but also on the specific context of each patient, their clinical conditions, and the capabilities of the local healthcare system. However, it is essential to mention that there is no single standard for use—choices are based on individual experiences and responses. For example, the drugs of choice for treating postoperative surgical hypertension include the administration of intravenous clevidipine, esmolol, NTG, and nicardipine. A systematic review and meta-analysis reported that clevidipine was the drug of choice for treating acute postoperative hypertension²⁹ (Table 3).

NTG

NTG is a pharmacological vasodilator primarily employed to alleviate angina crises in patients with chest pain and suspected acute myocardial infarction. The vasodilatory effects of NTG result from the release of nitric oxide, which induces venous vasodilation at low doses and arteriolar vasodilation at higher doses, reducing both pre- and afterload.^{30,31} Nitric oxide activates the enzyme guanylate cyclase, which converts guanosine triphosphate into cyclic guanosine monophosphate in vascular smooth muscle, inducing relaxation and consequent reduction in pre- and afterload.^{32,33} This effect is notable in the coronary circulation, where it significantly increases cardiac perfusion, making NTG ideal for angina treatment in the context of acute coronary syndrome^{31,34} and HE, such as acute heart failure, acute pulmonary edema,³⁵ and aortic dissection.³⁶ NTG is rapidly absorbed through the skin, mucous membranes, and gastrointestinal tract, being highly bioavailable.³¹ The sublingual tablet is the most common form of administration. Following administration, vasodilatory effects manifest within 1–3 minutes, with a peak action

at 5 minutes. The liver primarily metabolizes NTG and has a half-life of 2–3 minutes.²³ Other routes of administration include lingual (spray), sublingual (spray or tablet), topical (ointment or transdermal patch), and intravenous.^{37,38}

Adverse effects of NTG are primarily associated with the hypotensive impact of the drug. Patients may report symptoms of orthostatic hypotension, including dizziness, weakness, palpitations, and vertigo. Manifestations such as nausea, vomiting, sweating, pallor, and syncope can occur, even at therapeutic doses. Syncope is a significant risk, mainly when NTG is used with phosphodiesterase-5 (PDE-5) inhibitors.³⁹ In patients with occlusion of the right coronary artery, it is essential to exclude right ventricular infarction before administering NTG to prevent severe hypotension and cardiogenic shock.⁴⁰ NTG is contraindicated in patients with hypersensitivity to the drug, increased intracranial pressure, severe anemia, or myocardial infarction involving the right ventricle. Combining NTG with PDE-5 inhibitors, such as sildenafil, vardenafil, or tadalafil, is not recommended due to the increased risk of severe hypotensive effects and syncope.^{41,42} For patients with acute myocardial infarction or unstable angina pectoris and severe hypertension, intravenous esmolol is recommended, with intravenous NTG as an additional option if needed.⁴³ Importantly, care must be taken to avoid lowering the DBP below 60 mmHg with NTG infusion to prevent reduced coronary perfusion and aggravated myocardial ischemia (Table 3).

Beta-Blockers

Beta-blockers antagonize β -adrenergic receptors and are widely used in clinical practice. Their classification is based on selectivity for β -1 and β -2 receptors, intrinsic sympathomimetic activity, lipid solubility, vasodilatory potential, and distinct pharmacokinetics. Developed in three generations, the first includes non-selective agents like propranolol, which affect both β -1 and β -2 receptors. The second generation comprises drugs selective for the β -1 receptor, such as atenolol, bisoprolol, and metoprolol. The third generation encompasses drugs that may be selective or non-selective for the β -1 receptor and possess additional properties, such as α -1 receptor antagonism or the ability to induce nitric oxide production, expanding their applicability in medical practice.⁴⁴

Furthermore, patients with acute myocardial infarction or unstable angina pectoris and severe hypertension should be treated with intravenous esmolol⁴³. Beta-blockers should not be used for acute pulmonary edema treatment. For HE, excluding acute aortic dissection, BP should be reduced by approximately 20 to 25% within the first hour, then gradually lowered to 160/100 mmHg over the next 2–6 hours, and cautiously normalized over the following 24–48 hours^{45,46} (Figure 2, Table 3). Labetalol, a combined α - and β -blocker, is particularly effective in managing HE, including aortic dissection, hypertensive encephalopathy, eclampsia, and preeclampsia. Its rapid onset and dual administration routes (intravenous and oral) make it versatile, lowering BP safely without significantly reducing cardiac output or uteroplacental blood flow (Table 3).

Management of Specific Situations

a. Hypertensive Encephalopathy

Hypertensive encephalopathy is a neurological condition resulting from cerebral edema due to a sudden and/or sustained elevation of BP, often affecting patients with chronic hypertension. However, it can also occur in previously normotensive individuals. Impairment of cerebral autoregulation mechanisms is implicated in the etiology of this condition. Symptoms of hypertensive encephalopathy develop gradually, including headache, nausea, vomiting, and visual disturbances such as changes in visual fields, photopsia, blurred vision, visual hallucinations, mental confusion, coma, generalized seizures, and increased reflexes. Treatment aims for controlled and gradual BP reduction, as sudden and intense reductions can compromise cerebral blood flow and autoregulation capacity. In the management of hypertensive encephalopathy, the use of SNP is often recommended. In some contexts, other therapeutic options such as nicardipine, clevidipine, labetalol, or fenoldopam are also available and indicated. Additionally, it is advisable to initiate treatment with oral antihypertensive agents within the first 24–48 hours to ensure adequate BP control¹ (Figure 2, Table 3).

b. Acute Pulmonary Edema

Approximately one-third of patients hospitalized with acute pulmonary edema and HE have preserved left ventricular function, and myocardial ischemia

may play a relevant role in this case. In this severe context, ICU management is essential, involving intravenous medication, continuous monitoring, and gradual reduction of BP. The initial goal is to decrease mean arterial pressure by 20 to 25% in the first hours, avoiding sudden reductions that could lead to cerebral hypoperfusion.^{1,47} As vasodilators, NTG and SNP are employed to reduce both pre- and afterload. Loop diuretics are also used to decrease volume overload and BP. In certain situations, continuous positive airway pressure (CPAP) application may be beneficial in mitigating pulmonary edema and improving venous return¹ (Figure 2, Table 3).

c. Acute Coronary Syndrome

In coronary syndromes, an increase in BP can be observed as a response to myocardial hypoxia resulting from ischemia. This condition leads to an elevation in peripheral vascular resistance, intensifying myocardial oxygen demand. Therapeutic efforts focus on reducing cardiac workload without precipitating an increase in heart rate or a substantial reduction in preload, which could inadvertently elevate myocardial oxygen consumption. The therapeutic goal is to regulate SBP to remain below 140 mmHg, avoid reductions below 120 mmHg, and manage DBP to maintain levels within the 70–80 mmHg range. Given their pharmacological efficacy in modulating BP parameters, this balance can be achieved using medications such as esmolol, metoprolol, or NTG. Intravenous nitrates are a therapeutic option that reduces peripheral vascular resistance, improves coronary perfusion, and exerts a significant systemic vasodilatory effect, decreasing preload and myocardial oxygen consumption. The use of hydralazine, SNP, or nifedipine is generally discouraged due to the potential to cause suboptimal blood flow redistribution.⁶ Consequently, the clinical application of these medications is typically contraindicated, except in cases of severe hypertension in preeclampsia⁴⁸ (Figure 2, Table 3).

d. Acute Aortic Dissection

In suspected acute aortic dissection, the goal is to achieve a SBP below 120 mmHg and a heart rate below 60 bpm. The isolated use of SNP is not ideal, as it can increase heart rate and aortic ejection velocity, worsening the dissection. Therefore, it should be combined with a fast-acting, intravenously

adjustable beta-blocker. For asthmatic patients, non-dihydropyridine calcium channel blockers are a viable alternative. Intravenous opioid administration for pain control is also a critical strategy⁴⁹ (Figure 2, Table 3).

e. Hypertension in Pregnancy

In cases of severe hypertension during pregnancy, hospitalization is crucial to reduce BP to less than 160/105 mmHg and manage preeclampsia. Continuous cardiotocographic monitoring is necessary. The choice of antihypertensive medications varies depending on the diagnosis, proximity to delivery, the presence of preeclampsia, and the preferences and experience of the physician. Nifedipine is recommended for pregnant women with severe hypertension, while labetalol and hydralazine have limited effectiveness. In cases of severe preeclampsia or persistent or recurrent hypertension, intravenous administration of labetalol or urapidil is indicated. For mild preeclampsia or hypertension without preeclampsia, a multi-drug regimen is effective. Hydralazine is used only if labetalol or urapidil is not available or does not lower BP, and it should be avoided before delivery due to adverse perinatal effects. SNP is a last resort due to the risk of fetal cyanide poisoning. In preeclampsia with pulmonary edema, NTG is the drug of choice (Tables 3 and 4). For pregnant women in remote rural areas far from hospitals, a 10 mg short-acting nifedipine can be administered orally, with a second dose after one hour if necessary.³ Short-acting sublingual nifedipine is contraindicated. Women who experience hypertension during their first pregnancy are at a greater risk of developing hypertension and hypertensive disorders in subsequent pregnancies with an increased risk if hypertension occurs earlier in the first pregnancy^{3,11,50} (Figure 2, Table 3).

f. Preeclampsia

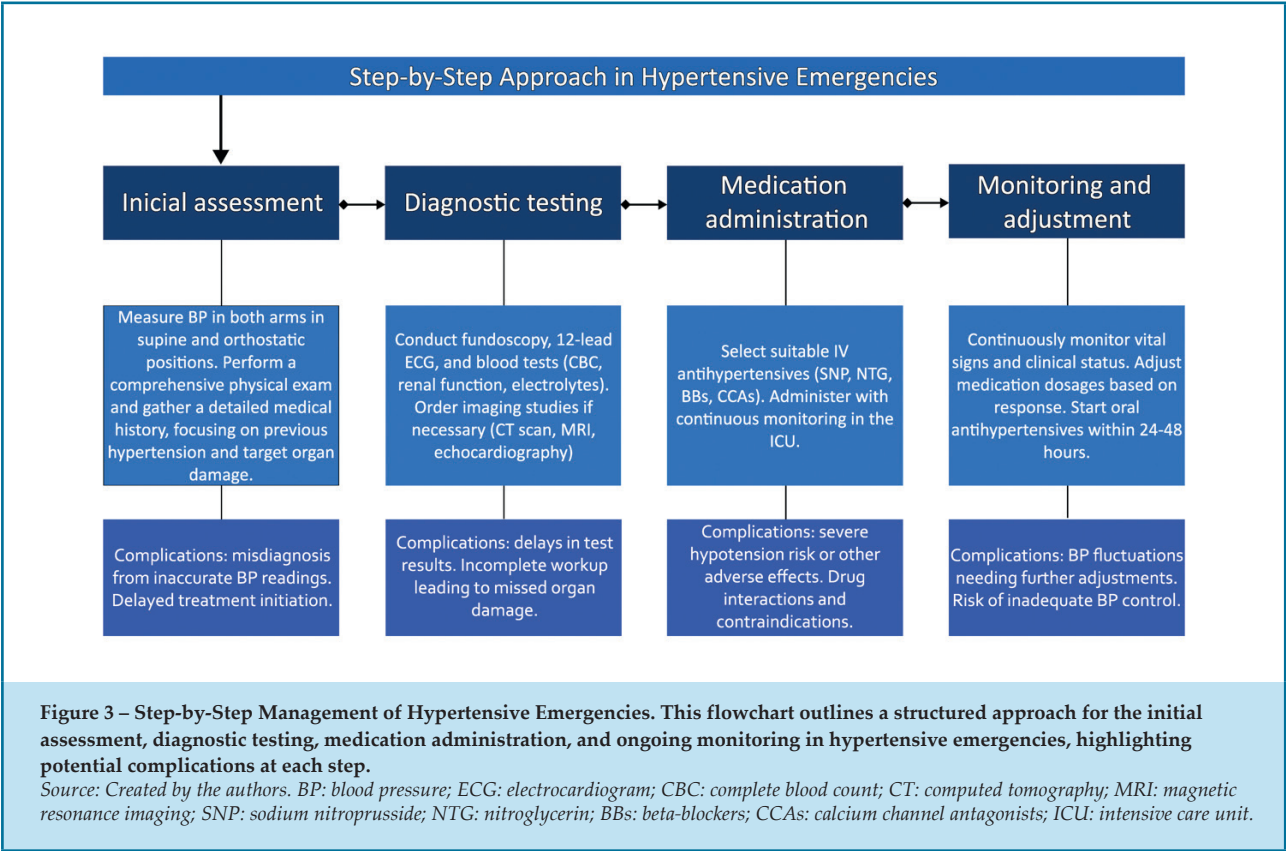
The treatment of severe hypertension in preeclampsia is crucial to mitigating maternal and fetal risks. Intervention becomes imperative when the SBP reaches 160 mmHg or the DBP reaches 110 mmHg. The American College of Obstetricians and Gynecologists endorses nifedipine, labetalol, and hydralazine as primary antihypertensive agents in these cases.⁴⁸ Nifedipine, a calcium channel antagonist, and labetalol, a beta-blocker, are preferred for their

effectiveness and safety. Hydralazine is traditionally used but cautiously due to the risk of inadequate blood flow redistribution. The choice of medication depends on clinical circumstances and availability of administration, with nifedipine being particularly beneficial when intravenous access is challenging. However, nifedipine is especially effective in reducing BP as monotherapy in eclampsia. In resource-abundant settings, hydralazine is preferred for hypertensive crises due to its rapid action and lack of rebound phenomenon. In resource-limited environments, nifedipine is recommended for its affordability and ease of administration, although monitoring after six hours is required to avoid rebound effects. The frequency of administration of these drugs is adjusted to local practices and current recommendations, emphasizing the customization of therapy to maintain adequate BP control and uteroplacental perfusion (Figure 2, Table 3).

Conclusion

HE require rapid diagnostic and therapeutic interventions to prevent severe organ damage

and reduce mortality risk. Effective management involves using intravenous medications tailored to the patient's clinical presentation and AOD. The structured approach depicted in Figures 2 and 3 guides assessment, medication administration, and monitoring in HE. Medications like NTG, calcium channel blockers, and beta-blockers each play specific roles depending on the clinical scenario, with careful consideration of their contraindications. Individualized treatment and close monitoring are crucial to improving outcomes. In Brazil, the public healthcare system primarily relies on sodium nitroprusside, labetalol, and hydralazine, facing limitations in accessing newer agents. The private sector offers a broader array, improving access to rapid treatment. Challenges in accurate BP assessment necessitate a comprehensive diagnostic approach, with repeated evaluations to confirm hemodynamic status. Ultimately, managing HE is a continuously evolving practice, requiring up-to-date knowledge, multidisciplinary collaboration, and ongoing professional education to ensure high-quality patient care.



Author Contributions

Conception and design of the research: Estado V; acquisition of data, analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual content: Silva MC, Costa-Filho RC, Estado V.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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